Int. J. Cancer: **119,** 1136–1144 (2006)

Brain cancer mortality and potential occupational exposure to lead: Findings From the National Longitudinal Mortality Study, 1979–1989

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We evaluated the association between potential occupational lead exposure and the risk of brain cancer mortality in the National Longitudinal Mortality Study (NLMS), which is a prospective census-based cohort study of mortality among the noninstitutionalized United States population (1979–1989). The present study was limited to individuals for whom occupation and industry were available (n = 317,968). Estimates of probability and intensity of lead exposure were assigned using a job-exposure matrix (JEM). Risk estimates for the impact of lead on brain cancer mortality were computed using standardized mortality ratio (SMR) and proportional hazards and Poisson regression techniques, adjusting for the effects of age, gender and several other covariates. Brain cancer mortality rates were greater among individuals in jobs potentially involving lead exposure as compared to those unexposed (age- and gender-adjusted hazard ratio (HR) = 1.5; 95% confidence interval (CI) = 0.9–2.3) with indications of an exposure–response trend (probability: low HR = 0.7 (95% CI = 0.2–2.2), medium HR = 1.4 (95% CI = 0.8–2.5), high HR = 2.2 (95% CI = 1.2–4.0); intensity: low HR = 1.2 (95% CI = 0.7–2.1), medium/high HR = 1.9 (95% CI = 1.0–3.4)). Brain cancer risk was greatest among individuals with the highest levels of probability and intensity (HR = 2.3; 95% CI = 1.3–4.2). These findings provide further support for an association between occupational lead exposure and brain cancer mortality, but need to be interpreted cautiously due to the consideration of brain cancer as one disease entity and the absence of biological measures of lead exposure.

Key words: lead; occupation; brain neoplasms; cohort studies

Exposure to lead compounds is predominantly due to anthropogenic activity,[1,2] and has long been suspected to result in chronic health effects.[1] The greatest potential for exposure has been experienced by industrial workers, and lead exposure is currently generally well controlled in major lead-using industries such as smelting and battery manufacturing industries.[1–3] A 5- to 10-fold decline in median and 75th percentile of lead exposure in general industry has been reported between 1979 and 1997.[4] Nevertheless, little to no decreases in lead exposure levels have been observed in certain work environments such as the construction industry,[4] and cases of clinical lead poisoning in certain industries still occur.[1] Historically, the largest source of environmental lead exposure in the United States was through inhalation and ingestion of air, dust, soil, water and food contaminated from the use of lead in pipes, paints, food and drink cans and gasoline. These uses have been phased out in many developed countries, and geometric mean blood lead levels among adults in the United States have declined from 13.1 μg/dL (0.63 μmol/L) in the late 1970s to 1.64 μg/dL (0.08 μmol/L) in 1999–2002.[5] However, sections of the general population continue to be exposed to excessive amounts of lead, especially from lead-based paints and contaminated soil in urban settings with an older housing stock.[5–13] Additionally, lead accumulates in the body which may become biologically available long after the occupational or environmental exposure has ceased.[2,14–16] Therefore, lead exposure is still a public health concern.

Although the etiology of brain cancer remains largely unknown,[17–21] there are several clues that exposure to lead may impact brain cancer risk. Lead has been shown to pass the blood–brain barrier,[22] which may result in elevated lead levels in brain tissue.[23] Lead is thought to play a facilitative role in carcinogenesis, involving inhibition of DNA synthesis and repair, oxidative damage and interaction with DNA-binding proteins and tumor suppressor proteins.[2,24,25] Additionally, brain tissues are reported to be relatively susceptible to oxidative stress and lipid peroxidation,[17] suggesting that the brain may be sensitive to the carcinogenic effects of lead. Experimental studies reporting an increased incidence of brain tumors in rats fed lead salts support this hypothesis.[26–28] On the other hand, the epidemiological literature for an association between lead exposure and brain cancer is inconclusive. Nonetheless, several studies evaluating brain tumor subtypes or relying on (semi-) quantitative measures of exposure reported findings indicative of an association.[29–34]

We assessed whether employment in occupations potentially involving exposure to lead compounds is related to an increased risk of mortality from brain cancer in the National Longitudinal Mortality Study (NLMS). The NLMS is a prospective census-based cohort study of mortality among the noninstitutionalized United States population, conducted by the National Heart, Lung, and Blood Institute in collaboration with the National Center for Health Statistics and the United States Bureau of the Census.[35,36]

Material and methods

Study population

The NLMS public-use data file consists of a national sample of the United States population (n = 637,162), as identified from the Current Population Survey (CPS) of the Bureau of the Census of March 1979, April 1980, August 1980, December 1980 and March 1981 (http://www.census.gov/nlms/). The full study is larger, involving 1.3 million persons,[35,36] but for confidentiality reasons, a subset of 5 samples closely reflecting the full NLMS database of the original 12 CPSs is provided for the limited access data set which is publicly available. All personal identifiers, geographical references, specific NLMS cohort references and specifically identifiable time components were removed from this public-use file. The present study is limited to individuals for whom occupation or industry codes were available, leaving a total of 317,968 individuals for the current analysis. Occupation or industry codes were missing for individuals who were not in the labor force (*i.e.*, age < 14 (45% of missing occupation or industry), home maker (27%), retired (16%), student (9%), inability to work (2%) or unemployed but actively looking for work (1%)). Records from the 5 CPS cohorts were matched to the national death index (NDI)

Abbreviations: CI, confidence interval; CNS, central nervous system; CPS, Current Population Survey; HR, hazard ratio; JEM, job-exposure matrix; NDI, national death index; NLMS, National Longitudinal Mortality Study; RR, rate ratio; RSMR, ratio of standardized mortality ratios; SMR, standardized mortality ratio.

Grant sponsor: Division of Cancer Epidemiology and Genetics, Intramural Research Program of the NIH, National Cancer Institute.

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Received 11 November 2005; Accepted 27 January 2006
DOI 10.1002/ijc.21947
Published online 28 March 2006 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – PERCENTAGE OF COMMON OCCUPATIONS AND INDUSTRIES AMONG INDIVIDUALS WITH POSSIBLE OCCUPATIONAL LEAD EXPOSURE[1]: NATIONAL LONGITUDINAL MORTALITY STUDY 1979–1989

Exposure level	Common occupations			Common industries		
	1970 Code	Title	%[2]	1970 Code	Title	%[2]
Probability						
Low (N = 12,763)	961	Firemen, fire protection	5.2	937	Local public administration	5.9
	153	Electrical and electronic engineering technicians	6.4	69	Special trade contractors	7.8
	430	Electricians	15.0			
	753	Freight and material handlers	19.4			
Medium (N = 27,718)	964	Policemen and detectives	5.1	937	Local public administration	5.4
	962	Guards and watchmen	6.5	417	Trucking service	9.3
	705	Deliverymen and routemen	6.7			
	602	Assemblers	13.9			
	715	Truck drivers	22.0			
High (N = 18,871)	623	Garage workers and gas station attendants	6.7	639	Motor vehicle dealers	5.3
	522	Plumbers and pipe fitters	7.5	648	Gasoline service stations	6.7
	321	Estimators and investigators, n.e.c.	8.0	757	Automobile repair and related services	8.3
	510	Painters, construction and maintenance	8.6	69	Special trade contractors	12.5
	680	Welders and flamecutters	12.1			
	481	Heavy equipment mechanics, incl. diesel	15.3			
	473	Automobile mechanics	16.9			
Intensity						
Low (N = 37,219)	705	Deliverymen and routemen	5.0	69	Special trade contractors	5.2
	430	Electricians	5.1	937	Local public administration	6.0
	753	Freight and material handlers	6.6	417	Trucking service	8.2
	602	Assemblers	10.3			
	715	Truck drivers	16.3			
Medium (N = 13,625)	492	Miscellaneous mechanics and repairmen	5.8	648	Gasoline service stations	6.7
	640	Mine operatives, n.e.c.	7.3			
	623	Garage workers and gas station attendants	9.3			
	321	Estimators and investigators, n.e.c.	11.0			
	680	Welders and flamecutters	16.7			
	481	Heavy equipment mechanics, incl. diesel	21.2			
High (N = 8,508)	530	Pressmen and plate printers, printing	5.7	639	Motor vehicle dealers	7.7
	422	Compositors and typesetters	6.5	339	Printing, publishing and allied industries, except newspapers	8.3
	644	Painters, manufactured articles	6.6	757	Automobile repair and related services	13.6
	190	Painters and sculptors	7.3	69	Special trade contractors	20.8
	522	Plumbers and pipe fitters	16.6			
	510	Painters, construction and maintenance	19.0			
	473	Automobile mechanics	37.6			

[1]Total individuals with potential lead exposure = 59,352 (18.7% of all 317,968 individuals in cohort).–[2]Percent of exposed individuals within each probability or intensity category.

to identify the occurrence and cause of death for each individual cohort member. Mortality follow-up in the public-use dataset was restricted to the period 1979–1989. Causes of death were classified according to ICD-9 codes; our analysis was limited to mortality from brain cancer (ICD-9 191).

Exposure assessment

Participants in the CPS employed at the time of the survey were asked about the job worked during the week preceding the survey. For persons unemployed but actively looking for work within the 4 week period prior to the survey, information was obtained for the most recent job held (if any) within 5 years of the survey.[37] Occupation and industry reported in the CPS were assigned 3-digit codes according to the 1970 US Bureau of the Census classification system of jobs and industries. On the basis of these codes, levels of exposure to lead were assigned to the current (for employed individuals) or most recent (for job seekers) job held, using a job-exposure matrix (JEM) for lead.[31] This JEM was previously developed by an industrial hygienist (M.D.) on the basis of information from the published literature, computerized exposure databases, unpublished industrial hygiene reports and the industrial hygienist's personal experience.[31] An estimate of intensity level (none = 0, low = 1, medium = 2, high = 3) and probability (none = 0, low = 1, medium = 2, high = 3) was assigned to each individual's 3-digit occupation and industry code. Intensity estimates reflected average blood lead levels of less than 0.9 (low intensity), 0.9–1.4 (medium intensity) and greater than 1.4 μmol/L (high intensity).[31] The probability of exposure was estimated on the basis of the proportion of exposed workers within a given job title or industry and the number of occupations or industries coded likewise.[38] If exposure was determined by the occupation itself regardless of industry, final intensity and probability scores were obtained by squaring the occupational scores. On the other hand, if exposure was determined by both occupation and industry, then the final probability and intensity score was based on multiplying the scores of occupation and industry.[31] Finally, the final probability and intensity scores were further grouped on the basis of 4 *a priori* selected categories (none = 0, low = 1–2, medium = 3–4, high = $\geq$6).[31] Almost 19% of cohort members (n = 59,352) were considered potentially exposed to lead in their jobs. An overview of occupations most commonly assigned possible lead exposure in this cohort is presented in Table I. The distribution of exposed jobs across levels of probability and intensity is shown in Table II.

TABLE II – DISTRIBUTION OF LEAD-EXPOSED JOBS BY LEVELS OF PROBABILITY AND INTENSITY: NATIONAL LONGITUDINAL MORTALITY STUDY 1979–1989

Probability level	Intensity level			Total
	Low	Medium	High	
Low				
Observed number of brain cancer deaths	3	0	0	3
Population at risk	12,096	664	3	12,763
Person-years	106,573.12	5,847.72	27.01	112,447.85
Medium				
Observed number of brain cancer deaths	13	0	0	13
Population at risk	24,656	1,391	1,671	27,718
Person-years	216,920.96	12,213.32	14,750.88	243,885.16
High				
Observed number of brain cancer deaths	0	10	3	13
Population at risk	467	11,570	6,834	18,871
Person-years	4,172.76	102,119.56	60,210.01	166,502.33
Total				
Observed number of brain cancer deaths	16	10	3	29
Population at risk	37,219	13,625	8,508	59,352
Person-years	327,666.84	120,180.60	74,987.90	522,835.33

Potential confounding factors

Several variables were considered potential confounders on the basis of previously identified risk factors, including gender, age, race, living in an urban area, marital status and educational level.[31] Age was categorized into 6 groups (<35, 35–44, 45–54, 55–64, 65–74 and >75 years of age), and race was classified as white or nonwhite. Residential location was classified as urban or rural according to the 1970 Census definition, where persons living in urbanized areas and places with a population of 2,500 or more outside urbanized areas were classified as urban dwellers; others were considered to be living in rural areas. Marital status was grouped into ever (currently married, separated, widowed or divorced) or never married, whereas 3 education levels were considered on the basis of the highest grade completed (less than high school, some high school or high school graduate and some college). Annual family income (<$15,000, $15,000–$24,999, >$25,000) was also considered as a potential confounder, but information on this variable was missing for almost 5% of individuals (n = 15,258). Therefore, we did not include income as a covariate in our analyses. However, results from analyses limited to individuals with information on all covariates (including income) were very similar to the findings presented here (data not shown).

Statistical analysis

The design of the public-use file is that the follow-up time starts for all records at the same hypothetical date and continues as indicated to mortality or censorship.[39] To be censored for this file means that the record was determined to be of a person alive at the end of the 9 years of follow-up. To assess the robustness of our findings to statistical assumptions inherent in the use of regression models, we evaluated the association between potential occupational lead exposure and brain cancer mortality with a variety of techniques to estimate the relative risk and corresponding 95% confidence interval (CI), including proportional hazards regression and grouped data analysis methods. Grouped data analyses included external adjustment methods using standardized mortality ratios (SMRs), and internal comparison rate ratios (RRs) using Poisson regression techniques. Findings from nonparametric Mantel–Haenszel RR analyses[40] were very similar to those from Poisson regression, and are therefore not reported here. Analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

Proportional hazards analysis

Initially, hazard ratios (HRs) and 95% CI comparing the risk of brain cancer among lead-exposed and unexposed individuals were estimated with the Cox proportional hazards model[41] (exact method) using the SAS PHREG procedure. Follow-up time was treated as the fundamental time variable, adjusting for the effect of age by covariate modeling on the basis of individuals' age at entry into the study.[42] A reduced regression model adjusted for the effects of age (continuous) and gender to facilitate comparison with the results obtained from the analysis of grouped data (see below). Furthermore, a full model was employed to control for age (continuous), gender (male or female), race (white or nonwhite), urban status (urban or rural), marital status (ever or never married) and education level (<any high school, some high school or some college). The full model only included individuals with complete information on all covariates; therefore, 2,106 subjects (0.7% of the eligible cohort) were excluded due to missing data. Results from the grouped data analysis and the reduced Cox proportional hazards regression model were very similar; therefore, only findings from the full Cox model are presented. The proportionality assumption for lead exposure and potential confounders was checked graphically by inspecting the log of the negative log of survival (*i.e.*, $\ln[-\ln|S(t)|]$) against survival time for the covariate categories after adjustment for other covariates.[39,43] If the proportionality assumption holds, the difference in $\ln[-\ln|S(t)|]$ over any 2 or more levels of the covariate should be approximately constant over the follow-up time period.[39,43] Although interpretation was limited due to sparse data, the log–log plots suggested that the proportional hazards assumption was violated for lead exposure and several other covariates. Therefore, we performed additional analyses of grouped data to assess the robustness of the association.

Analysis of grouped data

Several basic time indicators are needed to compute person-time for the analysis of grouped data in cohort studies, including date of birth, date of study entry and date of last observation.[44] This information was not available for the cohort members in the public-use file; therefore, these dates were created on the basis of the reported age at the time of survey, a hypothetical start of follow-up (assumed to be July 1, 1980 for all cohort members) and the number of days of follow-up (with a maximum of 9 years or 3,288 days). Date of birth was created by subtracting the age from the hypothetical start date, and by subtracting an additional 6 months to account for the variability in day of birth throughout a calendar year. For example, the birth date of an individual aged 20 at the start of follow-up (*i.e.*, July 1, 1980) was assumed to be January 1, 1960. The end of follow-up was determined by adding the number of days of follow-up to the hypothetical start date. That is, for a person alive at the end of 9 years of follow-up the end date was July 1, 1989.

Person-year data were generated according to the method described by Wood *et al*. using SAS in which time-dependent variables are accurately classified at each interval of observation.[44] Subsequently, SMRs were computed as the ratio of observed over expected brain cancer deaths, where the number of expected deaths

TABLE III – DESCRIPTIVE CHARACTERISTICS OF COHORT: NATIONAL LONGITUDINAL MORTALITY STUDY 1979–1989

Demographic variable	Unexposed				Exposed			
	Population-at-risk at baseline (%)	Person-years	Obs[1]	Crude rate ratio (95% CI)	Population-at-risk at baseline (%)	Person-years	Obs	Crude rate ratio (95% CI)
Total	258,616 (100)	2,288,835.41	90	–	59,352 (100)	522,835.33	29	–
Gender								
Men	127,757 (49.4)	1,122,964.24	48	1.0 (ref)	50,150 (84.5)	440,816.00	26	1.0 (ref)
Women	130,859 (50.6)	1,165,871.17	42	0.84 (0.56–1.28)	9,202 (15.5)	82,019.33	3	0.62 (0.19–2.05)
Age								
<35	132,141 (51.1)	919,305.78	6	0.05 (0.02–0.11)	30,527 (51.4)	209,119.19	2	0.06 (0.01–0.28)
35–44	47,343 (18.3)	511,682.25	7	0.10 (0.05–0.23)	11,424 (19.3)	123,323.20	5	0.26 (0.09–0.75)
45–54	39,886 (15.4)	373,033.21	12	0.24 (0.13–0.46)	9,055 (15.3)	86,959.64	6	0.44 (0.16–1.19)
55–64[2]	29,554 (11.4)	315,170.75	42	1.0 (ref)	6,675 (11.3)	70,392.44	11	1.0 (ref)
65–74	8,301 (3.2)	140,968.11	18	0.96 (0.55–1.66)	1,469 (2.5)	28,742.55	4	0.89 (0.28–2.80)
75+	1,391 (0.5)	28,675.32	5	1.31 (0.52–3.31)	202 (0.3)	4,298.32	1	1.49 (0.19–11.53)
Race								
White	228,631 (88.4)	2,024,076.00	83	1.0 (ref)	52,379 (88.3)	461,512.00	29	1.0 (ref)
Non-white	29,985 (11.6)	264,759.41	7	0.64 (0.30–1.39)	6,973 (11.8)	61,323.33	0	–
Urban status								
Urban	174,822 (67.6)	1,547,160.58	55	1.0	38,093 (64.2)	335,203.38	15	1.0
Rural	83,794 (32.4)	741,674.83	35	1.33 (0.87–2.03)	21,259 (35.8)	187,631.96	14	1.67 (0.80–3.45)
Marital status								
Never	67,068 (25.9)	598,974.97	10	1.0	13,360 (22.5)	119,096.00	1	1.0
Ever	189,573 (73.3)	1,672,181.31	80	2.87 (1.48–5.53)	45,861 (77.3)	402,571.22	28	8.28 (1.13–60.9)
Education[3]								
<Some HS	21,639 (8.37)	186,577.49	18	1.0	7,013 (11.8)	60,076.90	5	1.0
Some HS	137,641 (53.2)	1,219,557.79	37	0.31 (0.18–0.55)	38,984 (65.7)	344,258.91	15	0.52 (0.19–1.44)
>HS	99,238 (38.4)	881,826.95	35	0.41 (0.23–0.73)	13,330 (22.5)	118,296.84	9	0.91 (0.31–2.73)

[1]Observed number of brain cancer deaths.–[2]This age group was chosen as the referent category because it comprises the largest number of observed brain cancer deaths.–[3]HS, high school.

was based on 1980–1989 average mortality rates in the general United States population reported by the Centers for Disease Control and Prevention (http://wonder.cdc.gov). The 95% CIs were based on the Poisson distribution of the observed numbers of deaths.[45] Additionally, ratios of SMRs (RSMR) and corresponding 95% CIs were computed.[46] Finally, RRs and associated 95% CI were estimated with multivariate Poisson regression models using the SAS GENMOD procedure.[47,48] SMRs and RRs were adjusted for age (<35, 35–44, 45–54, 55–64, 65–74, >75) and gender (male or female).

Results

Descriptive characteristics of the current study cohort are shown by lead exposure status in Table III. Exposed and unexposed subjects were similar in most respects at baseline, *i.e.*, the majority was less than 35 years of age (51%), white (88%), lived in an urban setting (67%) and were married at baseline or had been married previously (74%). The distribution of gender and education differed somewhat by exposure status with exposed individuals more likely than unexposed subjects to be men (85% *vs.* 49%) and less educated (22.5% *vs.* 38.4% more than high school). Analysis of crude brain cancer rates among the unexposed showed an association with age (elevated rates in older people), marital status (married individuals at higher risk) and education (more educated subjects at lower risk). Crude RRs by gender, race and urban status demonstrated that men, whites and rural dwellers may be at increased risk (Table III).

Brain cancer mortality rates were greater among individuals in jobs potentially involving lead exposure, with a crude RR of 1.41 (95% CI = 0.93–2.14) comparing workers with any exposure to those without exposure. Adjustment for potential confounders either by proportional hazards or Poisson regression did not greatly impact this association (Table IV). The HR for the reduced and full model were 1.46 (95% CI = 0.94–2.26; data not shown) and 1.56 (95% CI = 1.00–2.43), respectively, whereas the Poisson regression RR was 1.42 (95% CI = 0.91–2.20). Regression analyses showed an exposure–response relationship between brain cancer risk and lead exposure, with rates increasing as probability and intensity of exposure increased (Table III). HRs or RRs were strongest when individuals with the highest levels of exposure (*i.e.*, high probability and medium/high intensity) were compared to those employed in jobs unlikely to involve lead exposure (reduced model HR = 2.28; 95% CI = 1.25–4.18, full model HR = 2.39; 95% CI = 1.29–4.41). As an alternative presentation of the exposure–response relationship, we also computed risk estimates for individuals in jobs with low probability and intensity (full model HR = 0.76; 95% CI = 0.24–2.41); low probability and medium/high intensity (no observed deaths); medium/high probability and low intensity (full model HR = 1.61; 95% CI = 0.89–2.94); and medium/high probability and intensity (full model HR = 2.06; 95% CI = 1.12–3.77).

Findings using SMRs instead of regression-based risk estimates were less clear-cut, with little indication of an elevated brain cancer risk among exposed subjects relative to the general United States population (SMR = 1.11; 95% CI = 0.74–1.59). Nevertheless, patterns of risk with increasing levels of exposure were similar to those observed with regression analyses. The ratio of SMRs comparing workers with the highest levels of exposure (*i.e.*, probability > medium and medium/high intensity) to those unexposed was only slightly lower than corresponding HR or RR estimates (RSMR = 1.66/0.87 = 1.91; 95% CI = 0.98–3.43).

Discussion

Despite decades of active epidemiological research, little progress has been made in conclusively identifying preventable risk factors for tumors of the brain and nervous system.[17–22,49] The prevalence of established risk factors (*i.e.*, therapeutic radiation, certain inherited genes[17–22,49]) in the general population is rare; therefore, these factors are of limited public health relevance to explain the majority of brain cancers or suggest preventive measures.[21,22] However, it has been suggested that moderate risks cannot be excluded for most occupational and environmental exposures.[18]

The epidemiological evidence for the carcinogenicity of lead has been reviewed on multiple occasions,[2,50–54] and is summarized in Table V. Steenland and Boffetta in 2000 considered 6 occupational cohort studies[29,30,58,60–63] particularly informative

TABLE IV – ADJUSTED RISK ESTIMATES AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN LEVELS OF OCCUPATIONAL LEAD EXPOSURE AND BRAIN CANCER MORTALITY: NATIONAL LONGITUDINAL MORTALITY STUDY 1979–1989

Exposure level	Population-at-risk	Person-years	Obs[1]	HR (CI)[2]	Analysis of grouped data[3]	
					SMR (CI)	RR (CI)
Not exposed	258,616	2,288,835	90	1.0 (ref)	0.87 (0.70–1.06)	1.0 (ref)
Any exposure	59,352	522,835	29	1.56 (1.00–2.43)	1.11 (0.74–1.59)	1.42 (0.91–2.20)
Probability						
Low	12,763	112,448	3	0.72 (0.23–2.30)	0.50 (0.10–1.47)	0.65 (0.20–2.06)
Medium	27,718	243,885	13	1.47 (0.81–2.68)	1.06 (0.56–1.81)	1.34 (0.74–2.43)
High	18,871	166,502	13	2.35 (1.28–4.32)	1.64 (0.87–2.80)	2.12 (1.17–3.87)
Intensity (any probability)						
Low	37,219	327,667	16	1.33 (0.77–2.31)	0.95 (0.54–1.54)	1.21 (0.70–2.09)
Medium/high	22,133	195,169	13	1.99 (1.09–3.66)	1.39 (0.74–2.38)	1.81 (0.99–3.29)
Medium	13,625	120,181	10	2.50 (1.27–4.92)	1.77 (0.85–3.25)	2.28 (1.17–4.44)
High	8,508	74,988	3	1.19 (0.37–3.80)	0.82 (0.17–2.39)	1.07 (0.33–3.40)
Intensity (probability > low)						
Low	25,123	221,094	13	1.61 (0.88–2.92)	1.16 (0.62–1.99)	1.48 (0.82–2.67)
Medium/high	21,466	189,294	13	2.05 (1.12–3.76)	1.44 (0.77–2.46)	1.87 (1.03–3.42)
Intensity (probability > medium)						
Low	467	4,173	0	–	0.00 (0.00–46.1)	–
Medium/high	18,404	162,330	13	2.39 (1.29–4.41)	1.66 (0.88–2.83)	2.21 (1.21–4.04)

[1]Observed number of brain cancer deaths.–[2]HR, hazard ratio; adjusted for age (continuous), gender (male or female), race (white or non-white), urban status (urban or rural), marital status (ever or never married), and education level (<any high school, some high school, some college)—complete case analysis including subject with complete information on all covariates (excluded subjects $n = 2{,}106$).–[3]SMR, standardized mortality ratio; RR, Poisson regression rate ratio; risk estimates adjusted for age (<35, 35–44, 45–54, 55–64, 65–74, >75) and gender (male or female).

with respect to brain cancer risk because of high documented exposures.[51] Some of these studies reported an elevated risk for brain cancer, in particular in the highest exposed subgroups,[29,61,62] whereas others found little evidence for an association.[58,60,63] They computed an overall relative risk of 1.06 (95% CI = 0.8–1.4) using meta-analytic techniques, and concluded that the evidence for excess brain cancer risk is weak despite some animal evidence. However, they pointed out that support for an association was provided by a death certificate-based study[31] and a case–control study of gliomas nested within an occupational cohort,[29] and concluded that ''brain cancer remains a concern.''[51] Several additional population-based studies reported an increased meningioma risk of about 2-fold or greater among subjects possibly exposed to lead.[32,34,69]

The results of this study were little affected by the analysis approach, and provide additional support for an association between occupational lead exposure and brain cancer risk. Brain cancer mortality rates were greater among those potentially exposed as compared to unexposed subjects, with indications of an exposure–response trend. Findings based on external comparison analysis were somewhat less indicative of an association, which may be due to a slightly favorable brain tumor mortality experience in our NLMS cohort as compared to the general United States population (SMR = 0.92; 95% CI = 0.76–1.10 based on 119 observed and 130 expected brain cancer deaths). However, SMR-based analyses also showed a positive exposure–response trend, and RSMR estimates were similar (albeit somewhat lower) to HR or RR estimates.

Analysis of crude brain cancer mortality rates indicated elevated rates in older people, and possible differential risk by marital status, education, gender, race and urban status although many of these associations were closer to the null after applying the full Cox proportional hazards model including all covariates and lead exposure status (data not shown). These risk factors were taken into account in the analysis to reduce the effect of a mixture of socioeconomic, lifestyle, environmental and occupational factors as well as diagnostic bias on the results.[31] Previous studies in the United States, Europe and China have been inconsistent regarding associations with rural dwelling[31,71] and educational level,[68,70,72–74] but findings have been indicative of an increased brain tumor risk among married individuals.[31,73]

Almost 19% of cohort members were considered potentially exposed to lead in their jobs for all probabilities and intensities combined, which is in line with prevalence estimates reported in other studies. For instance, death certificate-based investigations have reported prevalence estimates of ~20% among men[31] and 3% among women[32] in the United States using the same JEM. Furthermore, a lifetime prevalence of 47% of exposure to lead compounds was found based on expert review of work history questionnaires in a population-based case–control study conducted in Montreal, Canada from 1979–1985.[75] Other case–control studies carried out in the United States during the 1980s and 1990s reported prevalence estimates ranging from 4 to 36% based on self-report.[76–80]

Findings from this study (and many previous studies) must be interpreted in light of several limitations, including the consideration of all brain tumors as one entity, the absence of biological measures of exposure, and a small number of exposed subjects.

The classification of brain and central nervous system (CNS) tumors is complex, and consideration of histopathological characteristics is considered elementary.[81–83] The current WHO classification assigns morphology codes to 8 histological groups,[83,84] but meningioma and gliomas comprise more than 70% of all tumors. Meningioma is a predominantly benign tumor that arises from tissues surrounding the brain and spinal cord, and accounts for over 29% of all tumors.[83–86] Gliomas are tumors spanning a wide range of neoplasms with distinct clinical, histopathological and genetic features that arise from glial cells with a structural or supportive function.[83–86] Gliomas account for 42% of all tumors and 77% of malignant tumors.[84] Since different classes of brain tumors arise from distinct cell types, they may have different etiologies.[18] Consequently, real effects may be masked when diseases with different etiologies are studied as one disease, and future studies of brain tumors should focus on biologically distinct tumor types.[18] Our analysis addressed the association between occupational lead exposure and malignant brain tumors, since the number of deaths from malignant (ICD-9 192.1 and 192.3; $n = 1$) and benign (ICD-9 225.2 and 225.4; $n = 5$) meningiomas in the NLMS public-use data file was small. In addition to the complexity of classifying brain and CNS tumors, death certificates indicating brain cancer may reflect metastases from other sites[87] for which the exposure under study would not be relevant.

Exposure assessment was based on linking the occupation and industry reported by the subjects at baseline with a JEM previously developed based on information from the published literature, computerized exposure databases, unpublished industrial

TABLE V – SELECTED EPIDEMIOLOGICAL STUDIES OF (OCCUPATIONAL) LEAD EXPOSURE AND BRAIN CANCER[1]

First author (Year)	Country	Study population	Follow-up	Outcome	Exposure measure	Obs	RR (CI)
Cohort studies[2]							
Cooper (1985)[55]	The United States	2,300 lead production workers and 4,519 battery plant workers	1947–1980	Mortality (CNS)	Industry (SMR)		
					Lead battery plants	8	1.1 (0.5–2.1)
					Lead production facilities	3	0.9 (0.2–2.6)
Sweeney (1986)[56]	The United States	2,510 male tetraethyl lead workers	1952–1977	Mortality (brain)	Industry (SMR)	4	2.1 (0.7–4.9)
Sankila (1990)[57]	Finland	3,749 glass factory workers	1953–1986	Cancer incidence (CNS)	Industry (SIR)	6	0.6 (0.2–1.3)
Steenland (1992)[51,58]	The United States	1,990 male hourly lead smelter workers	1940–1988	Mortality	Industry (SMR)	NR	About 1.2
Cocco (1994)[59]	Italy	4,740 male lead and zinc miners	1960–1988	Mortality (CNS)	Industry (SMR)	8	1.2 (0.5–2.3)
Gerhardsson (1995)[60]	Sweden	664 male lead battery workers	1969–1989	Mortality and cancer incidence (CNS)	Industry (SIR)	1	0.8 (0.0–4.2)
Anttila (1996)[29,30]	Finland	Nested case–control study of 26 CNS tumors (16 gliomas) and 200 controls within a cohort of 20,741 workers biologically monitored for blood lead 1973–1983	1973–1988	Cancer incidence	Highest blood lead ($\mu mol*l^{-1}$; OR)		
				CNS	0.8–1.3	9	1.4 (0.5–4.1)
					1.4–4.3	10	2.2 (0.7–6.6)
				Glioma	0.8–1.3	8	6.7 (0.7–347)
					1.4–4.3	7	11 (1.0–626)
Cocco (1997)[61]	Italy	1,388 workers and laborers in production/maintenance departments in lead smelting plant	1950–1992	Mortality (brain)	Industry (SMR)		
					National reference	4	1.3 (0.3–3.2)
					Regional reference	4	2.2 (0.6–5.6)
Lundstrom (1997)[62]	Sweden	3,979 primary smelter workers including 1,992 lead-exposed workers	1955–1987	Mortality (CNS)	Lead-exposed workers (SMR), highest exposed subgroup	4	1.6 (0.4–4.2)
Wong (2000)[63]	The United States	4,518 workers at lead battery plants and 2,300 at lead smelters	1947–1995	Mortality (CNS)	Industry (SMR)	15	0.7 (0.4–1.2)
Englyst (2001)[64]	Sweden	3,979 lead smelter workers	1958–1987	Cancer incidence (CNS)	Lead subcohort 1 (SIR)	1	0.6 (0.0–3.6)
					Lead subcohort 2 (SIR)	0	0.0 (0.0–6.5)
Jemal (2002)[65]	The United States	3,592 white males and females from NHANES II 1976–1980	1976–1992	Mortality (brain)	Blood lead levels (RR) >50 percentile	5	0.5 (0.1–5.8)
Navas-Acien (2002)[33,34]	Sweden	1,779,646 men and 1,066,346 women gainfully employed in 1970	1971–1989	Morbidity (glioma and meningioma)	Lead exposure (SIR) Possible exposure (JEM)		
					Glioma	10	1.1 (0.6–2.0)
					Meningioma	7	2.4 (1.1–5.0)
Wesseling (2002)[66]	Finland	413,877 women with blue collar occupations in 1970	1971–1995	Cancer incidence (CNS)	Lead (SIR)		
					Low exposure	NR	1.3 (1.0–1.6)
					Med/high exposure (JEM)	NR	1.3 (0.9–2.0)
Case–control studies[2]							
Mallin (1989)[67]	The United States	1,212 deceased cases and 3,198 deceased noncancer controls	1979–1984	Brain	Glassworkers (white males)	8	3.0 (NR)
Cocco (1998)[31]	The United States	27,060 deceased cases and 108,240 deceased noncancer controls	1984–1992	Brain	Caucasian men (JEM): high probability, high intensity lead exposure	14	2.1 (1.1–4.0)
Hu (1998)[68]	China	218 cases and 436 controls	1989–1995	Glioma	Lead exposure (self-report)	0	–
Cocco (1999)[32]	The United States	12,980 female deceased cases and 51,920 female deceased noncancer controls	1984–1992	CNS	Any lead exposure (JEM)		
					CNS cancer	366	1.1 (1.0–1.2)
					Meningioma	9	1.9 (1.0–3.9)
Hu (1999)[69]	China	183 cases and 366 controls	1989–1996	Meningioma	Lead exposure (self-report)		
					Men	6	7.2 (1.0–52)
					Women	10	5.7 (1.4–23)
Carozza (2000)[70]	The United States	476 cases and 462 controls	1991–1994	Glioma	Foundry/smelter workers	6	2.6 (0.5–13)
					Painters	10	1.6 (0.5–4.9)

[1]Obs, observed number of exposed cases; NR, not reported;–[2]Cohort studies: measure of association = standardized mortality or incidence ratio (SMR, SIR), rate ratio (RR) or Odds ratio (OR; for nested case–control studies); Case–control studies: measure of association = Odds ratio (OR); CI = 95% confidence interval.

hygiene reports and personal experience.[31] This approach enabled us to elucidate exposure–response relationships by evaluating associations across strata of probability and intensity. However, these exposure estimates can only be considered crude surrogates for biological measures of exposure, such as bone lead levels,[15] since the current job at baseline may not be representative of the subjects' work history. Nonetheless, Gomez-Marin *et al*. recently found that current occupation can be used as a surrogate for longest-held job for many occupational subgroups,[88] including skilled jobs potentially involving elevated levels of lead exposure.

The possibility of confounding by occupational exposures other than the one under study is another concern when relying on job titles or JEMs. For example, jobs assigned high-probability and medium/high-intensity lead exposure included gas station attendants, painters, welders, plumbers and automobile mechanics. Furthermore, 8 out of 13 brain cancer deaths in the medium/high intensity category occurred among those employed as automobile mechanics (2 deaths; 28,302 person-years), heavy equipment mechanics (3 deaths; 25,331 person-years) and welders and flame-cutters (3 deaths; 20,177 person-years). These job titles are individually possibly associated with brain cancer mortality with a full model HR of 2.30 (95% CI = 0.56–9.56), 3.15 (95% CI = 0.97–10.20) and 5.12 (95% CI = 1.58–16.61), respectively. On the other hand, the remaining occupations in the medium/high intensity category showed little evidence for an increased brain cancer risk (full model HR = 1.02; 95% CI = 0.32–3.26). These 3 occupations may also involve exposure to aromatic hydrocarbons, metal fumes and electromagnetic fields.[31,89] Therefore, we cannot confidently rule out potential confounding although the impact on the observed associations is likely to be small because these co-exposures have only been inconclusively linked with brain cancer risk.[19,21,90]

Finally, past epidemiological studies generally reported only on a small number of exposed brain cancer cases (*e.g.*, $n < 10$), thereby resulting in statistically unreliable risk estimates (Table IV). Because of the large size of the NLMS cohort eligible for the current study ($n = 317{,}968$), we observed 29 exposed brain cancer deaths, and 13 deaths were assigned high-probability and medium/high-lead exposure. This number is larger than that in many previous studies, and yielded risk estimates that were generally quite precise. Nevertheless, we considered the number of lead-exposed brain cancer deaths insufficient to reliably assess effect modification with other potential occupational risk factors, such as exposure to extremely low-frequency electromagnetic fields.[33]

In conclusion, this study provides further suggestive evidence for a role of lead exposure in the development of brain cancer. Future studies evaluating this association should focus on different brain tumor subtypes and biological measures of lead exposure.

Acknowledgements

The authors thank Dr. R. Hoover for helpful suggestions. This paper uses data supplied by the National Heart, Lung, and Blood Institute, NIH, DHHS from the National Longitudinal Mortality Study. The views expressed in this paper are those of the authors and do not necessarily reflect the views of the National Heart, Lung, and Blood Institute, the Bureau of the Census or the National Center for Health Statistics.

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